Docket No.: 204372000301 (PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Lynn E. SPITLER and Anthony E. MAIDA, III

Application No.: 09/300,978

Filed: April 28, 1999 Art Unit: 1644

For: PROSTATIC CANCER VACCINE Examiner: P. Gambel

REPLY TO EXAMINER'S ANSWER

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is in response to the Examiner's Answer mailed September 9, 2003 (Paper No. 31), for which the time to reply expires on November 9, 2003. As November 9, 2003 is a Sunday, it is believed that this reply is timely filed on the next business day, November 10, 2003.

Appellants appreciate the opportunity to reply to the Examiner's Answer. The Reply Brief relates to claims directed to anticancer vaccines containing a host prostate antigen, namely PSMA and PAP, which antigen is shared with a tumor inhabiting the host tissue but is overexpressed in normal prostate tissue. The vaccine elicits an immune response against the prostate tumor and normal prostate tissue.

Appellants gratefully acknowledge the withdrawal of the rejection of the claims under 35 U.S.C. § 112, first paragraph with respect to nucleic acid sequences as they read on the known PAP and PSMA antigens of the claimed methods.

The Examiner has maintained one ground of rejection, reflected in issue 1, in which the claims stand rejected under 35 U.S.C. § 103(a). The Examiner asserts that the cited references regarding passive immunotherapy and humoral immunity teach or suggest active immunotherapy using prostate antigens. The remainder of this reply brief is concerned with showing that this conclusion has no scientific basis.

It is believed that issue 1 should be resolved in favor of appellants for the following reasons.

Issue 1: Obviousness of antitumor methods

In the Examiner's Answer, the Examiner maintains that "PSMA reads on Spitler's teaching of eliciting antitumor responses to prostate tumor antigens." Nevertheless, the remaining 13 references are cited to cure the acknowledged deficiency in Spitler - the absence of any specific teaching or suggestion for the use of the PSMA antigen. To summarize, the Examiner asserts in his Answer that (A) Appellants have improperly argued the references individually, (B) the term "tumor associated antigen" as used by Spitler encompasses PSMA, (C) the combination of references is proper in spite of the distinct biological basis for active and passive immunotherapy, and (D) pan-antigens (or epitopes) were unlikely and unknown at the time of filing. Appellants respectfully traverse these assertions.

A. <u>References have not been argued individually</u>

Appellants strongly object to the Examiner's assertion that the references have been argued individually. Appellants have, and continue to, examine the primary reference, Spitler, with great care as the rejection maintained by the Examiner seems to rest largely on Spitler's disclosure of active immunotherapy using various tumor antigens. According to all of the Actions to date, most of the numerous secondary references cited are simply to cure the acknowledged deficiency in Spitler, the lack of a disclosure of the antigens, *i.e.*, PSMA and PAP, of the instant claims. Each of the references has been, and continues to be, argued with regard to the teaching and suggestions of the reference when combined with Spitler. Aspects of Appellants' previous arguments are emphasized *infra* for the benefit of the Examiner.

B. The term "tumor associated antigen" as used by Spitler does not encompass PSMA

Appellants respectfully submit that the "tumor associated antigen" as used by Spitler does not encompass PSMA. As evident from the references cited by the Examiner, the term "tumor associated antigen" can include antigens that are also expressed at low levels on normal tissues. Thus, the definition asserted by the Examiner, and purportedly by Spitler, does not include antigens such as PSMA. PSMA is an antigen that is overexpressed on normal prostate tissue as well as prostate tumor. The distinctive nature of this class of antigens, and this antigen in particular, lies in that overexpression in normal tissues. It is evident to one of ordinary skill in immunology that an antigen that is overexpressed in normal tissue as well as tumor tissue typically is not a desirable target for immunotherapy for at least two reasons. First, an antigen that is overexpressed on normal tissue is seen by the host immune system as a "self" antigen. Thus, eliciting an active immune response requires breaking immunological tolerance, a difficult and unpredictable process. Second, once an active response is elicited to this "self" antigen, the activated immune effector cell will target tumor and normal tissue equally. Thus, the normal tissue, and in this particular case the entire organ, will be destroyed by the host's own immune response. By and large, this is not a problem if the antigen is expressed at low levels in normal tissues and is certainly not a problem if the antigen is expressed on normal tissue at a different, and non-concurrent, stage of differentiation. Antigens expressed at low levels on normal tissue and at increased levels on tumors offer better immunological targets because (1) breaking tolerance is less problematic, and (2) the antigen-expressing normal cells are typically not targeted as readily due to lower immunogenicity resulting from lower antigen expression.

As a result of this critical distinction, one of ordinary skill in immunology would not recognize PSMA as an antigen as being within the disclosure of Spitler or the other cited references relating to tumor associated antigens. In fact, at least one of the cited references makes this very distinction. Grauer states "[t]he diagnostic and therapeutic value of such tumor-associated antigens generally results from the excess quantity of antigen expressed by tumor cells relative to normal cells and the in vivo selectivity of antibodies for antigens expressed by tumor cells over normal

cells." *See* column 1, lines 40-45 (emphasis added).[1] An antigen that is overexpressed in normal tissue does not fit this definition as both tumor and normal cells will be targeted equally by antigen-specific immunotherapy. Therefore, PSMA and other antigens overexpressed on prostate tissue do not come within the definition of "tumor associated antigen" given by the references of record. In fact, when the cited references are carefully analyzed, it is clear that the tumor associated antigens known in the art are those with very little expression on normal tissue. The Examiner has not yet pointed to a single reference where the tumor antigen is one that is overexpressed in normal tissue.

Appellants note that the Examiner strenuously defends the definition of tumor-associated antigen as set forth in Cruse, Kuby and Paul. *See* pages 12-14 of Paper No. 31. Appellants emphatically object to the continued assertion of Cruse against the instant claims. Cruse has a publication date of 1995, and therefore is **not a proper prior art reference**. As such, it has been and continues to be asserted against the instant claims in complete disregard to well-established patent law and patent procedure. The Examiner is clearly seeking to muddy the waters with the use of an improper reference to define a term in Spitler. Appellants further note that it is clear that, regardless of the cited definitions, a dictionary definition alone is **not dispositive** on the meaning of a term. *See Anderson v. Int'l Eng'g & Mfg., Inc.*, 48 U.S.P.Q.2d 1631, 1634 (Fed. Cir. 1998) ("A word describing a patented technology takes its definition from the context in which it was used by the inventor.") A dictionary definition can be used so long as it does not contradict any definition found in or ascertained by a reading of the patent document. *See Gart v. Logitech, Inc.* 59 U.S.P.Q.2d 1290 (Fed. Cir. 2001). Hence, there is no legal basis for the unilateral substitution of a dictionary definition, including an improperly cited one, by the Examiner.

Appellants submit that Spitler does not disclose prostate tumor antigens that are overexpressed on normal prostate tissue. The disclosure in Spitler's summary of invention points only to tumor antigens expressed on a wide variety of tumors, including prostate tumors. The only mention of prostate tumor antigens is as follows:

> Of particular interest are liposome compositions encapsulating the TAAs CO-029, associated with tumors of the gastrointestinal tract, colorectal, and pancreas, and

[1] Appellants note that the disclosure of the Grauer reference is limited to passive immunotherapy using antibodies specific for the disclosed antigen.

> GA733-2, associated with tumors of the gastrointestinal tract, prostate, cervix, ovary, bladder, lung, breast, colorectum, and pancreas.

Spitler, column 2, lines 21-26 (emphasis added). This passage does not generically disclose prostate antigens as asserted by the Examiner. A known antigen, GA733-2, is disclosed as being expressed on prostate tumors. This antigen is also expressed on a number of other tumors and thus is not overexpressed in normal prostate tissue as are the antigens of the claimed methods.

Appellants are surprised to learn that the arguments regarding the organ-specific nature of the antigens at issue is a modification of our position. The instant specification discloses the organ-specific nature of the antigens at page 4, lines 9-22, stating that :

> While the prior art suggests the use of antigens uniquely associated with tumor tissue as components of antitumor vaccines, there appears to be no suggestion to use antigens which are uniquely represented on host tissue for the tumor. Since the prostate is not an essential organ, elimination of the prostate gland, which may be a concomitant effect of the vaccines of the invention, does not adversely impact the general health of the subject. Thus, prostate cancer offers a unique opportunity for treatment with vaccines which characterize the host organ itself, rather than the malignant or metastatic nature of the cells per se.

In fact, the organ-specific nature of the antigens and the expression on normal prostate tissue has been addressed in every almost every response to date. Nonetheless, the organ-specific nature of the antigens in the instant claims to date has been ignored by the Examiner.

C. The cited references fail to establish prima facie obviousness because at least the combination of references is improper

Appellants maintain there is neither motivation to combine the cited references with Spitler nor a reasonable expectation of success for such a combination. The Examiner continues to insist that disclosure regarding antibodies to prostate antigens and passive immunotherapy using antibodies provides sufficient motivation to combine these references with Spitler's teachings regarding active immunotherapy. This is simply incorrect.

Briefly, Claims 13, 15, 16, and 18-24 were rejected as obvious under 35 U.S.C. § 103 (a) over the combination of Spitler in view of Israeli *et al.*, Horoszewicz, Andriole *et al.* and in view of

the art acknowledged methods of delivering antigens of interest to stimulate antitumor responses and in further evidence of McCarley *et al.* alone or in combination with Cruse *et al.*, Kuby, Paul, Grauer, Varki, Linnenbach (the '254 patent), Linnenbach (the '002 patent), and Sela *et al.* Spitler discloses antitumor vaccine compositions and methods useful for the prevention and treatment of a variety of cancers, using tumor antigens that are associated on multiple tumor types. Israeli discloses a form of passive tumor immunotherapy, *i.e.*, therapeutic agents comprising an antibody directed to PSMA that is conjugated to a cytotoxic agent. Horoszewicz relates to passive immunotherapy using prostate-specific antibodies with a limited disclosure regarding active immunotherapy using prostate-specific anti-idiotype antibodies. Andriole relates to various forms of treatment for prostate cancer other than immunotherapy. McCarley discloses antibodies against prostate antigens that are useful in passive immunotherapy. Grauer and Varki relate to the generation of antigen-specific antibodies that may be useful in passive immunotherapy. The '254 patent discloses a tumor antigen that is expressed on multiple tumor types, *i.e.*, a pan-antigen (or pan-epitope). The '002 patent relate to a specific tumor antigen found on multiple tumor types and not on normal tissues. Cruse, Kuby, and Paul relate to the various groupings of tumor antigens. Sela relates to antibodies binding a tumor antigen expressed on multiple gastrointestinal tumors.

References disclosing PSMA antibodies and/or passive immunotherapy employing PSMA fail to provide any motivation for a combination with Spitler, or any reasonable expectation for success for such a combination. Appellants submit that the skilled artisan would not be motivated to combine the teachings of references that teach or disclose distinct biological processes such as passive and active immunotherapy.

It is well known that passive and active immunotherapy are distinct and separate biological processes. For example, this distinction is recognized in the classic text CANCER: PRINCIPLES & PRACTICE OF ONCOLOGY (De Vita et al., eds. 1993). It states that "[s]trategies for the immunotherapy of cancer can be divided into active and passive approaches." *Id.* at page 305. Active immunotherapy is described as "immunization of the tumor-bearing host with materials designed to elicit an immune reaction capable of eliminating or retarding growth." *Id.* Typically, this involves the development of cellular response to the tumor. Passive immunotherapy, on the

other hand, is the administration of exogenous antibodies.[2] *Id.* at Table 17-12. Thus, two critical and undeniable distinctions arise. First, active immunotherapy requires the participation of the host immune response, while passive immunotherapy does not. Thus, antigens that may serve as effective targets for passive immunotherapy may in fact be completely non-immunogenic if the same antigen is administered to the host. Such *in vivo* factors as available antigen presenting cells, suppressive cytokines, lack of appropriate co-stimulatory molecules, and identity as self-antigens can contribute to the lack of immunogenicity of such an antigen to its host's immune system.

Second, it is well recognized that humoral and cellular components of the immune system are not superimposable on each other.

> There is a significant difference in the nature of antigens recognized by humoral and cellular detection systems. Humoral antibodies detect specific epitopes on antigenic molecules, and it is the interaction of these molecules with the variable region of the antibody that produces recognition. In contrast, antigens recognized by T-cell receptors recognize processed peptides on the surface of the tumor cell or on an antigen presenting cell in conjunction with MHC molecules.

Id. at page 301. Effective active immunotherapy protocols typically elicit a cellular response to the immunizing antigen. Thus, the ability to generate antibodies to PSMA or the suggestion to use such antibodies in passive immunotherapy has no relevance to the instant claims drawn to methods of active immunotherapy of prostate cancer. These recognized distinctions between active and passive immunotherapy and between antibody and T-cell receptor recognition are still cornerstones of tumor immunotherapy today. Moreover, many of the antibodies disclosed in the cited references are of non-human origin. Therefore, they contain no teaching whatsoever regarding the immunogenicity of the same antigen in humans, a critical element of any active immunotherapy strategy. A person of ordinary skill in the art would not be motivated to combine these references because of these well known distinctions. Therefore, the teachings relating to antibodies in Horoszewicz, McCarley, Grauer, Varki or Israeli do not provide any motivation to combine or any reasonable expectation of success.

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[2] Passive immunotherapy can also include the exogenous administration of other immune effectors, such as activated lymphocytes. However, such passive immunotherapy still does not require the active participation of the host immune response.

The disclosure of anti-idiotype antibody immunotherapy strategy in Horoszewicz does not cure the deficiency in Spitler. The use of anti-idiotype antibodies in Horoszewicz provides no teaching or suggestion regarding the use of antigens overexpressed in normal host tissues in active immunotherapy. Anti-idiotype antibodies are distinct from antigen-based therapies in at least three aspects: (1) anti-idiotype antibodies elicit an antitumor response to a single epitope of the antigen, *i.e.*, the binding cleft of the antibody, whereas antigen administration results in response to multiple epitopes; (2) anti-idiotype antibodies do not require processing and presentation by antigen presenting cells, whereas antigen administration is completely dependent on appropriate processing and presentation by antigen presenting cells; and (3) anti-idiotype antibodies are typically foreign to the host, while the instant prostate antigen is self antigen overexpressed on normal host tissue. The person of ordinary skill in immunology recognizes each of these as significant, distinct, and non-overlapping when considering immunotherapy.

The remaining references do not remedy the deficiencies in Spitler for reasons already of record. Appellants note that Andriole actually teaches away from the need for immunotherapy, as acknowledged by the Examiner in his answer. *See* Paper No. 51, page 7 (stating that Andriole teaches that "surgical excision of the prostate is unsurpassed as a means of controlling organ-confined prostate cancer.").

Appellants note that not one of the many references cited by the Examiner, or any combination of those references, teaches, discloses, or suggests the use of antigens overexpressed in normal prostate tissue to induce an active immune response against normal and malignant cells that results in the equivalent targeting of tumor and normal cells, and subsequently the ablation of an entire organ.

D. Pan-antigens in cancer were neither unknown or unlikely at the time of filing

Appellants submit that the characterization of Spitler as being drawn to using a single cancer antigen to vaccinate against all cancers is neither unlikely or unknown to one of skill in the art at the time of filing. In point of fact, the primary antigen taught by Spitler, *i.e.*, GA733-2, is an antigen expressed on a wide variety of tumors. GA733-2 was initially given various different names based

on the monoclonal antibodies first identifying the antigen including KSA, KS1/4, and CO 17-1A. *See, e.g.*, Litivinov et al., *J. Cell Biol.* 125: 437-446 (1994); Fornaro et al., *Int. J. Cancer* 62: 610-18 (1995) (discussing GA733-2 and GA733-1 antigens); and Balzar et al., *J. Mol. Med.* 77: 699-712 (1999). Now known as Ep-CAM, this antigen is still known as one widely expressed on a majority of human carcinomas. *See* Balzar at page 699, second column, first full paragraph. Similarly, CO-029, another antigen specifically cited by Spitler, also is expressed on a wide variety of cancers. *See e.g.*, Salza et al., *Proc. Natl. Acad. Sci. U.S.A.* 87: 6833-37 (1990). This information was known to one of skill in the art at the time of filing. In order to accept the argument asserted by the Examiner, one has to assume that the knowledge of such antigens would not lead the skilled artisan to suggest and pursue such a strategy. To date, no objective evidence has been provided to demonstrate that one of skill in the art considered such a vaccine strategy unlikely. Therefore, Appellants submit that there has been no mischaracterization of the type of antigen disclosed by Spitler.

The antigens disclosed by Spitler are uniquely associated with the cancer, *i.e.*, malignant, phenotype. In other words, the antigens are unique in their expression or association with a number of malignant cells that differ in histologically and genetically. These antigens were frequently clustered together and are unique as antigens that are expressed on a wide variety of cancers. The characterization of these antigens as uniquely associated with the malignant phenotype is accurate and reflects the knowledge in the art at the time of filing and today. The Examiner has not presented any objective evidence that these antigens are not uniquely associated with the malignant phenotype. Appellants again submit that these antigens represent pan-antigens (or pan-epitopes) for carcinomas generally and are unique in their expression on a variety of malignant cells. Spitler teaches the use of antigens that are pan-antigens (or pan-epitopes) for malignant cells throughout the disclosure with ever suggesting the use of a organ-specific antigen.

In summary, there is no valid scientific basis that supports the combination of references cited by the Examiner. The reasoning cited by the Examiner flies in the face of years of well established scientific dogma regarding known intricacies of tumor immunity. Reversal of this basis for rejection is therefore requested.

Conclusion and Request for Oral Hearing

For the reasons stated above, Appellants respectfully request that the rejection under 35 U.S.C. § 103 (a) for obviousness be reversed and claims 13, 15, 16, and 18-24 passed to allowance.

An oral hearing is requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Appellants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 204372000301.

Dated: November 10, 2003

Respectfully submitted,

By _____

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